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# Mathematical Considerations on Multi-Cellular Developmental Systems (情報科学の数学的基礎理 論と応用)

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MATHEMATICAL CONSIDERATIONS ON  
MULTI-CELLULAR DEVELOPMENTAL SYSTEMS

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1 Introduction

Multi-cellular organisms like filamentous plants, early embryos, nervous systems, neuro-muscular systems, retino-tectal systems and other systems of various complexity levels, are considered to emerge from origin cells through successive unequal cell divisions. Upon the philosophy that the processes of cell proliferation and interconnection are deterministically controlled by division history of each component cell, we proposed a mathematical theory of developmental processes [1], [2]. We did not consider cell migration and growth explicitly. These papers contain biological foundation and discussion as well as theoretical results.

In this paper, let us develop further mathematical analysis of our cell lineage and connection relation system (CLR system) in the framework of automata theory.

2 Preliminary Explanations

For the sake of simplicity, let us assume throughout in this paper that the alphabet used for identifying each cell is binary, i.e.  $B=\{a,b\}$ . This constraint brings into no loss of mathematical generality.

2.1 CL System

A cell lineage system (CL system) is a pair  $(B, \mathcal{D})$ , where  $\mathcal{D}$  is the division time spectrum satisfying the following conditions:

- (1)  $\mathcal{D}$  is a family of mutually disjoint subsets of  $B^*$ . That is,

$$\mathcal{D} = \{D_0, D_1, D_2, \dots, D_i, \dots\},$$

where  $D_i$ 's are called components of  $\mathcal{D}$  and especially  $D_0$  the terminal component.

(2) For every  $i$ , if  $w=uv \in D_i$ , then there is a non-terminal component  $D_j$  (depending on  $u$ ) such that  $u \in D_j$ .

Meaning of CL system: If  $w \in D_i$  with  $i \neq 0$ , then the cell having the division history  $w$  bifurcates in  $i$  units of time and its daughters obtain those of  $wa$  and  $wb$ . If  $w \in D_0$ , then the cell  $w$  never divides.  $\lambda$  is the origin cell (a spore or a fertilized egg). A CL system is often identified with its division time spectrum  $\mathcal{D}$ .

Finite Regular CL Systems: When the number of components of  $\mathcal{D}$  is finite and every component is a possibly empty regular set on  $B$ , then the system is called a finite regular CL system. In the following we treat this kind of CL systems mainly.

## 2.2 Rational Relations

$(B^*, \cdot)$  and  $(N, +)$  are monoids, whose unit elements are  $\lambda$  and  $0$  respectively, where  $N$  is the set of nonnegative integers.

A subset  $R$  of  $B^* \times N$  is called a rational relation in  $B^* \times N$ , if  $R$  is defined by means of a rational machine  $M$  as follows:

$$M = (Q, f, q_0, F)$$

where  $Q$  is the finite set of states,

$f$  is the set of nondeterministic transitions defined by arcs  $q \xrightarrow{(x,n)} q'$ , where  $x \in B_\lambda$

$= B \cup \{\lambda\}$  and  $n \in N$ , and  $(x,n) \neq (\lambda,0)$ ,

$q_0$  is the initial state and

$F$  is the set of accepting states.

$w \in B^* \times N$  is called to be accepted by  $M$ , if  $q_0 w \cap F \neq \emptyset$ , where  $q_0 w$  means the set of states which are reached through a path from  $q_0$ . Paths are defined as usual by means of the juxtaposition of operations in the product monoid  $B^* \times N$ . The relation defined by a rational machine  $M$  is denoted by  $R(M)$  and defined by

$$R(M) = \{ w \in B^* \times N \mid q_0 w \cap F \neq \emptyset \}.$$

$R$  is called a rational relation if there is a rational machine  $M$  such that  $R = R(M)$ .

In the similar way, rational relations in  $B^* \times B^* \times N$  are defined by means of rational machines.

Note that the above defined notion of rational relation is essentially the same as the "transduction" defined by Elgot and Mezei [3] and the "rational relation" by Eilenberg [4].

### 2.3 Semi-direct Product

Let  $R$  and  $S$  be relations in  $B^* \times N$ . Then the relation in  $B^* \times B^* \times N$   $T = \{ (w, v, n) \mid n \in N, (w, n) \in R \text{ and } (v, n) \in S \}$  is called the semi-direct product of  $R$  and  $S$  and denoted by  $R \oslash S$ .

#### Proposition 1

If  $R$  and  $S$  are rational relations in  $B^* \times N$ , then their semi-direct product  $T$  is also rational.

#### Proof

Let  $M_R$  and  $M_S$  be rational machines defining  $R$  and  $S$ , respectively. From  $M_R$ , for example, by adding new states, construct a "canonical" rational machine

$M_R'$  such that  $R(M_R')=R$  and every transition arc is labeled with  $(x,1)$  where  $x \in B_\lambda$ . That is, if  $q \xrightarrow{(x,n)} q'$

is an arc of  $M_R$ , then it is replaced by a chain of arcs  $q \xrightarrow{(x,1)} q_1 \xrightarrow{(\lambda,1)} q_2 \rightarrow \dots \rightarrow q_{n-1} \xrightarrow{(\lambda,1)} q'$ . Every augmented state is a non-accepting state.

Now the rational machine  $M_T$  is constructed from  $M_R'$  by making the "product" machine as follows: The state set is  $Q_R \times Q_S$ , where  $Q_R$  and  $Q_S$  are those of  $M_R$  and  $M_S$ , respectively. An arc  $(p,q) \xrightarrow{(x,1)} (p',q')$  is

drawn in  $M_T$ , whenever arcs  $p \xrightarrow{(x,1)} p'$  and  $q \xrightarrow{(x,1)} q'$  are

in  $M_R$  and  $M_S$ , respectively.  $F_T = F_R \times F_S$  and  $q_{0T} = (q_{0R}, q_{0S})$ . From this construction of  $M_T$ , it will be clear that  $R(M_T) = T = R \circ S$ . Q.E.D.

### Proposition 2 [3]

If  $R \subseteq B^* \times B^* \times N$  is rational, its projections to the components  $R_1 = \{ w \mid (w,v,n) \in R \}$  and so on are regular sets on  $B$ .

### Proof

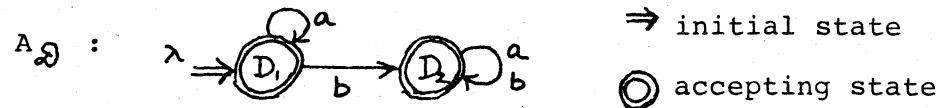
Clear from the definition of rational machines.

### 3 Cell Proliferation Process

Suppose that a finite regular CL system  $(B, \mathcal{D})$  is given with  $\mathcal{D} = \{D_0, D_1, \dots, D_k\}$ . Then construct a finite automaton  $A_{\mathcal{D}}$  as described in Nishio [1], which defines the family of regular sets  $D_i$ 's. Note that no arc emerges from the states defining  $D_0$ .

Example 1 (defining automaton of CL system)

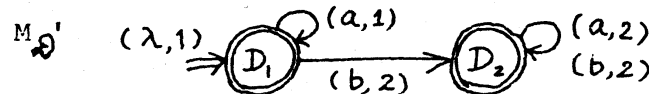
$\mathcal{D} = \{D_1, D_2\}$ , where  $D_1 = a^*$  and  $D_2 = B^* - a^*$



Next, from  $A_{\mathcal{D}}$ , we construct a corresponding rational machine  $M_{\mathcal{D}}'$  by taking into account the division time. Indeed, attach the division time  $i$  to an arc of  $A_{\mathcal{D}}$ , if it enters a state accepting  $D_i$ . Then it is clear that  $M_{\mathcal{D}}'$  defines a (rational) relation  $R_{\mathcal{D}}'$  in  $B^* \times N$  such that if  $(w, n) \in R_{\mathcal{D}}'$ , the cell  $w$  is produced by the CL system  $\mathcal{D}$  at time  $n$ .

Example 2 (rational machine)

CL system is the same as in Example 1.

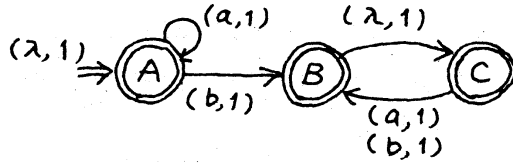


Finally, as is described in the proof of Proposition 1, canonical machine is constructed from  $M_{\mathcal{D}}'$  and every state is defined to be an accepting state. Furthermore, from a state defining  $D_0$ , if any, an arc with label  $(\lambda, 1)$  is drawn to itself. Denote this machine by  $M_{\mathcal{D}}$ . Then,

$$R(M_{\mathcal{D}}) = R(M_{\mathcal{D}}') \cup \{(w, n+j) \mid (w, n) \in R_{\mathcal{D}}' \text{ and} \\
j=1, \dots, i-1 \text{ if } w \in D_i \text{ and} \\
j=1, 2, \dots \text{ if } w \in D_0\}$$

Example 3 (modified canonical machine)

$M_{\mathcal{D}}$  corresponding to  $M_{\mathcal{D}}'$  in Example 2.



Meaning of  $R(M_{\mathcal{D}})$ : If  $(w,n) \in R(M_{\mathcal{D}})$ , then the cell  $w$  exists at time  $n$ . Let us call  $R(M_{\mathcal{D}})$  or simply  $R_{\mathcal{D}}$  the proliferation relation of CL system  $\mathcal{D}$ .

Next the cell population at time  $t$  is given by

$$W_t = \{ w \mid (w,t) \in R \}.$$

$$W = W_0, W_1, W_2, \dots, W_t, \dots$$

is called the proliferation process of  $\mathcal{D}$ , Nishio [2].

#### 4 Connectability Relation and Developmental Process

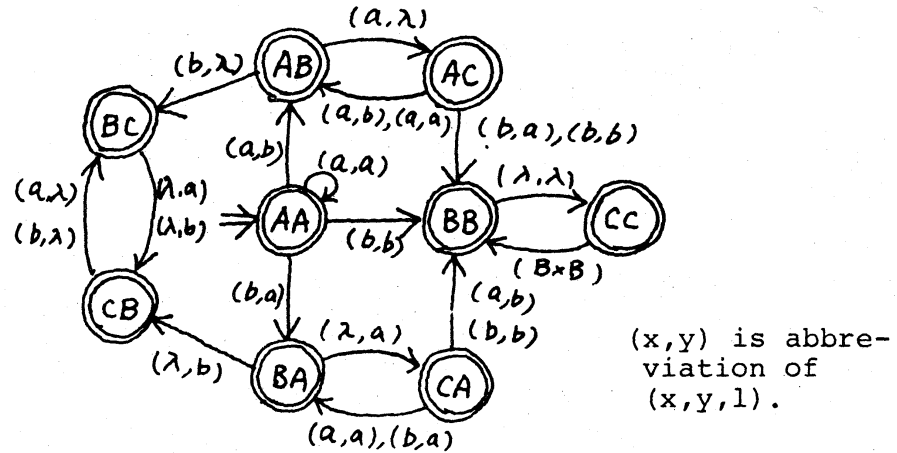
A connectability relation is a rational relation  $S \subset B^* \times B^* \times N$ . It is considered to be given a priori from some biological ground and is interpreted as follows: If a pair of cells  $w$  and  $v$  exist at time  $t$  and  $(w,v,t) \in S$ , then  $w$  is connected to  $v$  at time  $t$ . Contrarily, even when  $(w,v,t)$  is in  $S$ , a connection from  $w$  to  $v$  is not established if  $w$  or  $v$  is not in  $W_t$ . Note that this interpretation of instant emergence of a connection is biologically questionable in cases where spacially separated cells are to be connected after migration and growth. But, for the sake of simplicity, we dare adopt it in this analysis.

Now let  $R_{\mathcal{D}}$  be the proliferation relation derived from a CL system  $\mathcal{D}$  as in Section 3. Then the semi-direct product  $R_{\mathcal{D}} \otimes R_{\mathcal{D}}$  is a connection relation among cell population produced by  $\mathcal{D}$ , such that there exists

a connection between every pair of cells. So, the relation  $R \otimes \Theta R$  will be called the perfect connection relation.

Example 4 (perfect connection relation)

$M_{R \otimes \Theta R}$ , where  $M_R$  is given in Example 3.



Relation describing developmental processes:

Now we define our final relation  $r$  in  $B \times B \times N$ .

$$r = S \cap R \otimes \Theta R$$

where  $S$  is a rational connectability relation. Obviously  $r$  is a relation describing a process of cell proliferation and connection in the following sense. If  $(w, v, t) \in r$ , then the cell  $w$  is connected in reality to  $v$  at time  $t$ . Thus,  $r$  represents the developmental process generated by a developmental system  $G = (B, \Theta, S)$ , where  $(B, \Theta)$  is its CL system and  $S$  is a connectability relation.  $G$  is called a CLR system too.

## 5 Some Results on Properties of $r$

In general the set of rational relations is not



closed under intersection [3]. But there had remained the problem to determine, whether  $r$  is always rational or not, since  $R \circ R$ 's constitute a special class of rational relations in  $B^* \times B^* \times N$ . Indeed we obtained

Theorem 1

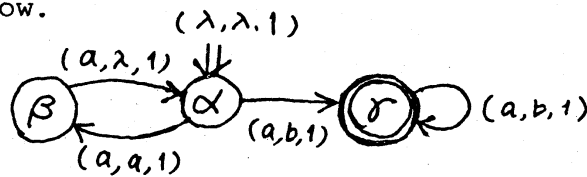
There is a developmental system  $G = (B, \mathcal{D}, S)$  with  $\mathcal{D}$  finite regular and  $S$  rational, such that

$$r_G = S \cap R \circ R$$

is not a rational relation.

Proof

We show an example of  $G$  which satisfies the theorem. Let  $\mathcal{D}$  be as given in Example 1 and  $S$  be defined by  $M_S$  below.



Clearly,  $S = \{(a^{2i+j}, a^i b^j, 2i+j) \mid i \geq 0 \text{ and } j \geq 1\}$ .

Note that  $R \circ R$  is defined by the machine illustrated in Example 4. Then,

$$r_G = \{(a^{3i}, a^i b^i, 3i) \mid i \geq 1\}.$$

Since  $\{a^i b^i \mid i \geq 1\}$  is not a regular set,  $r_G$  is not a rational relation from Proposition 2. Q.E.D.

For filamentous organisms (see [1]), we have the following theorem.

Theorem 2

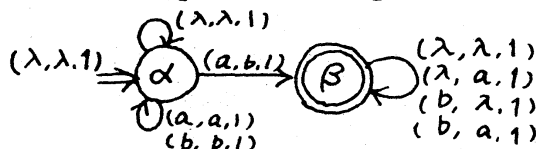
Let  $R_f$  be the filamentous connectivity relation, i.e.  $R_f = \{wab^*wba^*t \mid w \in B^* \text{ and } t \in N\}$ . (see [2]).

Then, for an arbitrary finite regular CL system  $\mathcal{D}$ ,

$$r_f = R_f \cap R_{\mathcal{D}} \circ R_{\mathcal{D}} \quad \text{is a rational relation.}$$

Proof

$R_f$  can be represented by the following machine  $M_f$ .



We denote a machine defining  $R_{\mathcal{D}} \circ R_{\mathcal{D}}$  by  $M_D$ . Now we construct a rational machine  $M_r$  which represents  $r_f$ .

First of all, the state set of  $M_r$  is defined to be the direct product of those of  $M_D$  and  $M_f$ . Of  $M_D$ , suppose there is an arc going from the state  $q$  to  $q'$  and having the label  $(x, x, 1)$  where  $x \in B_\lambda$ . Then in  $M_r$  an arc is drawn from state  $(q, \alpha)$  to state  $(q', \alpha)$  with label  $(x, x, 1)$ . If in  $M_D$  there is an arc going from  $q$  to  $q'$  with label  $(a, b, 1)$ , then  $M_r$  has an arc from  $(q, \alpha)$  to  $(q', \beta)$  with the same label. Finally, if in  $M_D$  arcs from  $q$  to  $q'$  with labels  $(\lambda, \lambda, 1)$ ,  $(\lambda, a, 1)$ ,  $(b, \lambda, 1)$  or  $(b, a, 1)$  <sup>exist</sup>, then in  $M_r$  an arc from  $(q, \beta)$  to  $(q', \beta)$  with the respective label is defined.

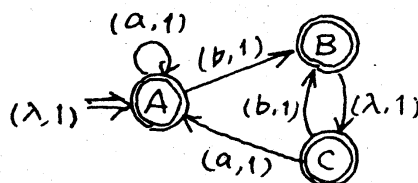
The initial state of  $M_r$  is  $(q_0, \alpha)$  where  $q_0$  is that of  $M_D$  and the accepting states are those which are of the form  $(q, \beta)$ .

Since in this construction of  $M_r$ , no pathological phenomenon, which might arise from the non-freeness of  $B^* \times B^* \times N$ , does not occur,  $M_r$  defines  $r_f$  in reality.

Q.E.D.

Example 5

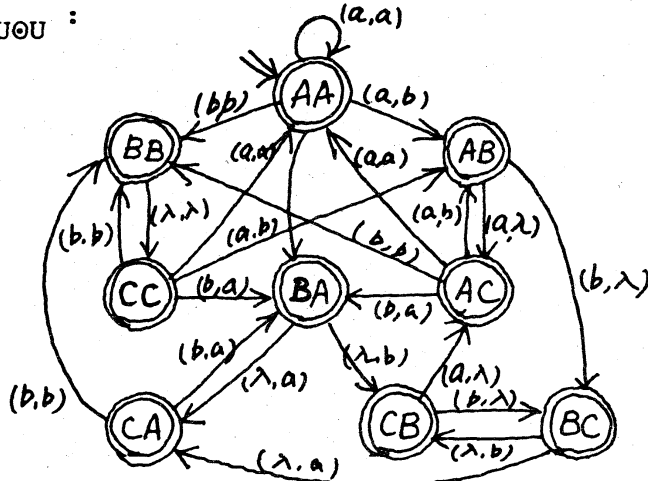
$M_{\mathcal{D}}$  :



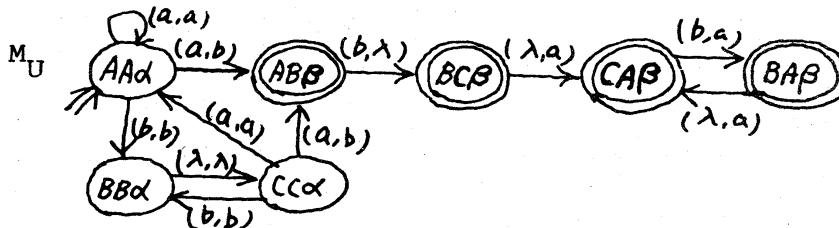
Example 5 continued.

$R(M_{\mathcal{Q}})$  is denoted by  $U$ .

$M_{U \cup U}$  :



$r_U = R_f \cap U \cup U$  is defined by the following  $M_U$ .



Significance of Theorem 1: In general a developmental process can not be represented by a finite state machine, while its generating system  $G$  is defined by rational machines. This is an example which would support the belief that to describe directly a mature organism is more complicated than to do its generating rule.

The following problems remain unsolved.

(1) Decision problem: for arbitrarily given finite regular CL system  $\mathcal{Q}$  and <sup>rational</sup>connectability relation  $S$ ,

decide whether the developmental process  $r$  is rational or not. We conjecture that it is unsolvable.

(2) Characterization problem: Investigate conditions for  $\mathcal{D}$  and  $s$  such that  $r$  is rational.

## 6 Positional Information in Filamentous Organisms

As described in [1], a filamentous organism without branches like a blue green alga *Anabaena* consists of a string of linearly connected cells. If we consider  $w_a$  as the apical and  $w_b$  the basal daughter produced by division of a cell  $w$ , a CLR system  $G_f = (B, \mathcal{D}, R_f)$  with the filamentous connectability relation  $R_f$  generates a time series of filamentous organisms. (In this section, we do not assume the regularity of  $\mathcal{D}$ ).

As the simplest case of positional information, let us consider the cells located at the center of an organism during the time course of development. So, we define and investigate the relation of central cells  $P_{1/2} \subset B^* \times N$ :

$$P_{1/2} = \{(w, t) \mid w \in B^*, t \in N \text{ and } w \text{ is located at the center at time } t\}.$$

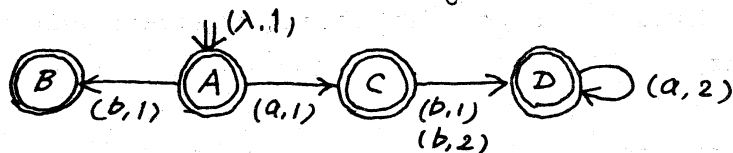
When an organism contains even number of cells at a time,  $P_{1/2}$  has two elements corresponding to this time.

We show some examples which might be useful for understanding properties of  $P_{1/2}$ . Proofs will be omitted.

### Example 6

The CL system is the same as in Example 1, i.e.  $D_1 = a^*$  and  $D_2 = B^* - a^*$ . Then,  $P_{1/2}$  is rational and

defined by the following machine  $M_6$ .



#### Example 7

$$D_1 = aB^* \cup \{\lambda\} \quad \text{and} \quad D_2 = bB^*$$

$$P_{1/2} = \{(\lambda, 0), (a, 1), (b, 1), (ab, 2), (aba, 3), (abb, 3)\}$$

$$\cup \{(\{aba^{t/2-1}ba^{t/2-2}, aba^{t/2}b^{t/2-2}\}, t) \mid t=2n, n \geq 1\}$$

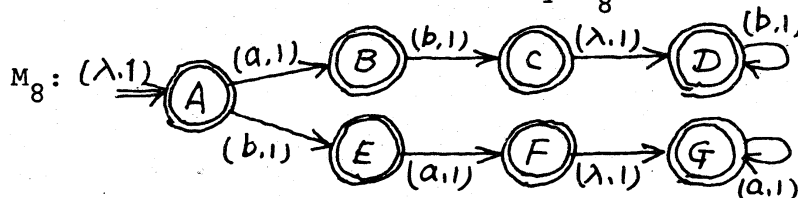
$$\cup \{(\{aba^{(t-1)/2-1}ba^{(t-1)/2-1}, aba^{(t-1)/2}b^{(t-1)/2-1}\}, t) \mid t=2n+1, n \geq 1\}$$

From Proposition 2, this  $P_{1/2}$  is not a rational relation.

#### Example 8

$$D_1 = B^* - D_2 \quad \text{and} \quad D_2 = \{a^i b^i, b^i a^i \mid i \geq 1\}.$$

This CL system is obviously finite nonregular. But,  $P_{1/2}$  is rational and indeed defined by  $M_8$ .



The decision problem that given an arbitrary finite regular CL system, decide if  $P_{1/2}$  is rational or not has not been solved.

As is  $P_{1/2}$ , for example, the "one third position"  $P_{1/3}$  from the apical end can be defined. As to rationality,  $P_{1/2}$  and  $P_{1/3}$  seem to have similar character, but this problem has not been studied.

The author thanks Y.Kobuchi, H.Okabe, S.Seki, T.Nishida and H.Doi for their interests and discussions.

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